DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

SIEMENS HEALTHCARE DIAGNOSTICS
KATHLEEN DRAY-LYONS
REGULATORY AFFAIRS SPECIALIST
500 GBC DRIVE
NEWARK DE 19714

November 4, 2015

Re: K150168
Trade/Device Name: Dimension Tacrolimus Flex® Reagent Cartridge (TAC)
Dimension Tacrolimus Calibrator (TAC CAL)
Regulation Number: 21 CFR 862.1678
Regulation Name: Tacrolimus test system
Regulatory Class: II
Product Code: MLM, JIT
Dated: October 30, 2015
Received: November 2, 2015

Dear Ms. Dray-Lyons:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulations (21 CFR Parts 801 and 809), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Katherine Serrano -S

For: Courtney H. Lias, Ph.D.
Director
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*
k150168

Device Name
Dimension Tacrolimus Flex® Reagent Cartridge (TAC)
Dimension Tacrolimus Calibrator (TAC CAL)

Indications for Use *(Describe)*
The Dimension Tacrolimus Flex® Reagent Cartridge (TAC) is an in vitro diagnostic test for the quantitative measurement of tacrolimus in human whole blood on the Dimension® clinical chemistry system. Measurements of tacrolimus are used as an aid in the management of tacrolimus therapy in renal and hepatic transplant patients.

The Dimension Tacrolimus Calibrator (TAC CAL) is an in vitro diagnostic product for the calibration of the Tacrolimus (TAC) method on the Dimension® clinical chemistry system.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 79 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

510(k) Summary

This summary of 510(k) safety and effectiveness information is submitted in accordance with the requirements of SMDA 1990 and 21 CFR §807.92.

The assigned 510(k) number is: **k150168**

1. **Submitter**

Siemens Healthcare Diagnostics Inc.
P.O. Box 6101
Newark, DE 19714

Tel: 302-631-9352
FAX # 302-631-6299

Contact Person: Anna Marie (Kathy) Ennis
Date of Preparation: September 23, 2015

2. **Device**

Name of Device:	Dimension Tacrolimus Flex® reagent cartridge (TAC)
Common Name:	Tacrolimus Assay
Classification Name:	Tacrolimus Test System (21CFR§862.1678)
Regulatory Class:	II
Product Code:	MLM

Name of Device:	Dimension Tacrolimus Calibrator (TAC CAL)
Common Name:	Tacrolimus Calibrator (TAC CAL)
Classification Name:	Calibrator Secondary (21CFR§862.1150)
Regulatory Class:	II
Product Code:	JIT

3. Predicate Device

Abbott® ARCHITECT Tacrolimus Test System - k070820

Dimension® Tacrolimus Calibrator – k060503

Reference Device: LC/MS –MS Assay for Tacrolimus

4. **Guidance Document(s):**

"Class II Special Controls Guidance Document: Cyclosporine and Tacrolimus Assays; Guidance for Industry and FDA" 11/16/2002

"Bundling Multiple Devices or Multiple Indications in a Single Submission"- 06/22/2007

"The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)] Guidance for Industry and Food and Drug Administration Staff" 7/28/2014

5. Device Description(s):

Dimension Tacrolimus Flex® Reagent Cartridge (TAC)

The automated Dimension® TAC method uses an immunoassay technique in which free and tacrolimus-bound antibody-enzyme conjugate is separated using magnetic particles. The assay is performed using a method specific Flex® reagent cartridge. The Flex® cartridge contains a pretreatment reagent, antibody-ß-galactosidase conjugate, tacrolimus immobilized on chromium dioxide particles, chlorophenol red ß-d-galactopyranoside (CPRG) substrate, and diluent to hydrate the tablets.To perform the TAC assay, a sample cup with a whole blood sample to be analyzed and a TAC Flex® reagent cartridge are placed appropriately on the Dimension® system. The
Dimension® system mixes and lyses the whole blood sample in the presence of pretreatment reagent 1. This reagent contains a displacer which acts to displace tacrolimus in the sample from binding proteins. The lysed sample is then mixed with the antibody enzyme conjugate. The tacrolimus present in the sample is bound by the tacrolimus antibody. Magnetic particles coated with tacrolimus are added to bind free (unbound) antibody-enzyme conjugate. The reaction mixture is then separated magnetically. Following separation, the supernatant containing the tacrolimus-antibody-enzyme complex is transferred to a cuvette and mixed with the substrate; chlorophenol red ß-d-galactopyranoside (CPRG). ß-galactosidase catalyzes the hydrolysis of CPRG to produce chlorophenol red (CPR) that absorbs light maximally at 577 nm. The change in absorbance at 577 nm due to the formation of CPR is directly proportional to the amount of tacrolimus in the patient's sample and is measured using a bichromatic (577, 700 nm) rate technique.

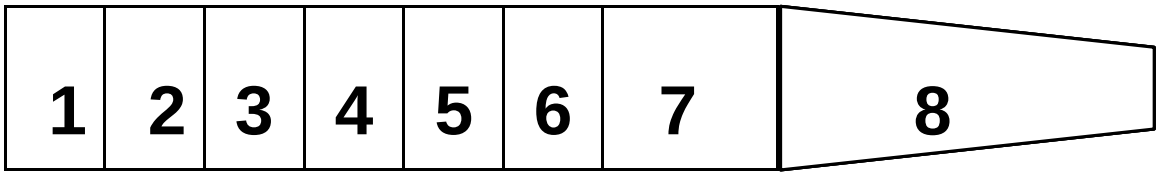
TACR+Ab-ß-gal ————> TACR-Ab-ß-gal + Ab-ß+gal

TACR-Ab-ß-gal + Ab-ß-gal + CrO2-TACR —(Magnetic separation)—> TACR-Ab-ß-gal (transferred to cuvette)

CPRG (non-absorbing at 577 nm) —TACR-Ab-ß-gal—> CPR (absorbs at 577 nm)

If the calculated tacrolimus concentration in the patient sample exceeds 20 ng/mL, the test is automatically repeated using pretreatment reagent 2 in place of pretreatment reagent 1. Pretreatment reagent 2 does not contain the displacer so the signal produced represents non-analyte signal. If significant signal is detected during the second analysis, the potential exists that interference from non-specific signal has impacted the accuracy of the initial test. In this situation, the reported test result is suppressed and replaced by a non-reportable test result message.

The reagents for the Tacrolimus assay are packaged in an 8-well Flex® Reagent Cartridge represented (top view) in the drawing below:



The reagent placement is as follows:

Reagent Placement Dimension® Tacrolimus Flex® Reagent Cartridge

Wells[a]	Form	Ingredient	Concentration[b]	Source
1	Liquid	Ab-ß-galactosidase	[c]	mouse, monoclonal
2	Liquid	Pretreatment reagent 2		
3,4	Tablets[d]	Tacrolimus-CrO2	36 mg/tab	
5,6	Tablets[d]	CPRG	9.3 mg/tablet	
7	Liquid	Substrate diluent		
8	Liquid	Pretreatment reagent 1		

a. Wells are numbered consecutively from the wide end of the cartridge.
b. Nominal value in hydrated cartridge.
c. Antibody titer and conjugate activity may vary from lot to lot.
d. Tablets contain excipients, buffers, and stabilizers.

Dimension Tacrolimus Calibrator (TAC CAL)

Dimension® Tacrolimus (TAC) Calibrator is five level frozen liquid, whole blood hemolysate containing purified tacrolimus. The product is provided in 4.0 mL vials, 2 vials per level. There are five calibrator levels per kit which span the assay range for the Dimension® Tacrolimus (TAC) assay. Calibrators are filled with 1.0 mL per vial except for Level 1 calibrator which contains 2.0 mL per vial.

6. Intended Use/ Indications for Use

Dimension Tacrolimus Flex® Reagent Cartridge (TAC)

The Dimension® Tacrolimus Flex Reagent Cartridge (TAC) method is an *in vitro* diagnostic test for the quantitative measurement of tacrolimus in human whole blood on the Dimension® clinical chemistry system.

Measurements of tacrolimus are used as an aid in the management of tacrolimus therapy in renal and hepatic transplant patients.

Dimension Tacrolimus Calibrator (TAC CAL)

The Dimension® Tacrolimus Calibrator (TAC CAL) is an *in vitro* diagnostic product for the calibration of the Tacrolimus (TAC) method on the Dimension® clinical chemistry system.

7. Comparison of Technological Characteristics

A comparison summary of the features of the products is included in the following table.

Item	Device **Dimension Tacrolimus Flex® Reagent Cartridge (TAC)**	Predicate **ARCHITECT Tacrolimus Assay (k070820)**
Similarities		
Intended Use	an *in vitro* diagnostic test for the quantitative measurement of tacrolimus in human whole blood	an *in vitro* diagnostic test for the quantitative measurement of tacrolimus in whole blood.
Indications for Use	used as an aid in the management of tacrolimus therapy in renal and hepatic transplant patients	used as an aid in the management of liver and kidney allograft patient receiving tacrolimus therapy
Sample Types	Whole blood in EDTA	Whole blood in EDTA
High Sample Dilution	Manual	Manual
Assay Type	Immunoassay	Immunoassay
Differences		
Instrument	The Dimension® clinical chemistry system.	The Abbott ARCHITECT ***i*** System
Sample Pretreatment	No manual pretreatment	Manual pre-treatment
Cross reactivity Profile		
M-I	1%	8%
M-II	18%	94%
M-III	15%	45%
M-IV	99%	9%
M-V	1%	Not Available
M-VI	1%	Not Available
M-VII	43%	Not Available
M-VIII	0%	Not Available
Measuring Range	1.0 – 30 ng/mL	2 – 30 ng/mL

Calibrator:

Item	Device Dimension Tacrolimus Calibrator	Predicate TACR CAL (k060503)
Similarities		
Intended Use	An *in vitro* diagnostic product for the calibration of the Tacrolimus (TAC) method on the Dimension® clinical chemistry system.	An *in vitro* diagnostic product intended to be used to calibrate the Tacrolimus method (TACR) for the Dimension® clinical chemistry system.
Form	Frozen Liquid	Frozen Liquid
Matrix	Whole blood hemolysate	Whole blood hemolysate
Levels	Five	Five
Traceability	Purified tacrolimus	Purified tacrolimus
Differences		
Assignment	Assigned for Dimension® TAC	Assigned for Dimension® TACR
Target Concentration Range	Level 1: - 0.5 to + 0.5 ng/mL Level 2: 2.7 to 4.2 ng/mL Level 3: 5.8 to 7.3 ng/mL Level 4: 11.6 to 13.6 ng/mL Level 5: ≥30.0 ng/mL	Level A: - 0.7 to + 0.7 ng/mL Level 2: 2.5 to 4.0 ng/mL Level 3: 5.5 to 7.0 ng/mL Level 4: 11.0 to 13.0 ng/mL Level 5: 31.0 to 34.0 ng/mL

8. Performance Data

Precision

Reproducibility testing was conducted for the Dimension ® TAC method, at two external evaluation sites in addition to our internal testing. This testing was done in accordance with the CLSI/NCCLS Approved Guideline for User Evaluation of Precision Performance of Clinical Chemistry Devices EP5-A2. Typical precision at levels ranging from a mean of 1.8 to 27.4 ng/mL was ≤ 6.6% CV for Repeatability and ≤ 13.1% CV for Within Lab.

Linearity

The analytical measuring range of the TAC method was confirmed by the establishment of the Limit of Quantitation (LoQ), for the low end, and by a linearity study. The linearity study was performed by mixing of a sample with a known native high tacrolimus concentration (40.3 ng/mL) with a normal patient pool with no tacrolimus in various ratios. The testing procedure was based on the CLSI Guideline EP 06-A Evaluation of the Linearity of Quantitative Measurement. A linear regression, and a 2nd - and 3rd -order polynomial regressions of the mean observed analyte values vs. expected concentrations were performed. The assay range for the Dimension® TAC method was established as 1.0 – 30.0 ng/mL by these two studies.

Specificity

Interference and cross-reactivity testing was performed according to *CLSI/NCCLS Approved Guideline Interference Testing in Clinical Chemistry: EP7-A2*. The compounds tested included endogenous compounds, drugs that are commonly co-administered with tacrolimus, and the anticoagulant EDTA. The cross-reactivity testing was done with major tacrolimus metabolite, M I (13-O-desmethyl-tacrolimus), M II (31-O-desmethyl-tacrolimus); as well as minor metabolites M III (15-O-desmethyl-tacrolimus), M IV (12-O-hydroxyl-tacrolimus), M V (15,31-O-didesmethyl-tacrolimus); and second pass metabolites, M VI (13,31-O-didesmethyl-tacrolimus), M VII (13,15-O-didesmethyl-tacrolimus) and M VIII(unknown name). Testing was done as recommended in the FDA Guidance document "*Class II Special Controls Guidance Document: cyclosporine and Tacrolimus Assays; Guidance for Industry and FDA" – 09/16/2002.* These studies showed that the Dimension® TAC method has low cross-reactivity to the major (M-1) tacrolimus metabolite,

and partial cross reactivity to the minor and second pass metabolites of lower prevalence. Co-administered drugs and other compounds tested for interference, exhibited less than 10% bias at the levels tested.

Recovery

The recovery capability of the Dimension® TAC assay was challenged across the assay range using samples spiked with USP tacrolimus. All samples met the acceptance criterion of ≤ 10% mean bias in recovery.

Method Comparison

A method comparison study was performed at two external evaluation sites and internally per the *"FDA Class II Special Controls Guidance document: Cyclosporine and Tacrolimus Assays; Guidance for Industry and FDA".* Samples included a nearly equal distribution of liver and kidney transplant patients which covered >80% of the assay range (1.0 – 30 ng/mL). CLSI Guideline EP-9A2 "Method Comparison and Bias Estimation using Patient Samples" was used to develop the study design.

As recommended by the guidance, samples were evaluated, at two external sites as well as internally, versus the predicate, ARCHITECT Tacrolimus Assay (k070820), and an LCMS reference method. An additional comparative method, Dimension® TACR, was also run at two sites. Analysis was done by Passing – Bablok regression. Least Squares regression was used to compute the correlation coefficient.

Dimension Tacrolimus (TAC) method vs	Slope	Intercept	r	n	Range (ng/mL)
Reference Method LC-MS/MS	1.04	-0.30	0.966	315	1.3-24.9
ARCHITECT Tacrolimus Assay (k070820)	0.99	-0.42	0.979	308	2.1-24.2
Dimension Tacrolimus (TACR) method (k060502)	1.00	-0.50	0.957	213	2.6 – 21.7

The samples range for the proposed Dimension TAC assay, in these studies, was 1.2 – 25.6 ng/mL.

Calibrator Traceability

Siemens Tacrolimus (TAC) Calibrator is traceable to purified tacrolimus drug through standardization of the LC-MS/MS reference method with gravimetrically prepared standards.

Calibrator Stability

Unopened vials of Siemens Tacrolimus (TAC) Calibrator are stored frozen (-25 to -15 ºC) until the expiration date printed on each carton. Once thawed, assigned values are stable for 30 days when recapped immediately after use and stored at 2-8°C.

9. Conclusion:

The Siemens Healthcare Diagnostics Dimension® TAC method and the ARCHITECT Tacrolimus Assay (k070820) are substantially equivalent based on their intended use, indications for use and performance characteristics. In performance studies, summarized above, the Dimension® Tacrolimus methods demonstrated performance similar to the predicate ARCHITECT Tacrolimus Assay (k070820).

The modified Siemens Healthcare Diagnostics Dimension ® TAC calibrator and the predicate Dimension® TACR calibrator (K060503) are also substantially equivalent in design, intended use, principle and performance.

Anna Marie Kathleen Ennis
Regulatory Affairs Manager